Systematic review and meta-analysis of surgical interventions versus conservative therapy for venous ulcers

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Objective: **This goal of this study was to systematically review the literature to determine if surgical intervention (open or endovascular) is superior to compression alone with respect to ulcer healing, ulcer recurrence, and time to ulcer healing in patients with lower extremity venous ulcer disease.**

Methods: **We conducted a comprehensive search of multiple databases for randomized controlled trials (RCTs) and comparative observational studies from 1990 to December 2013. The interventions of interest were any open or endovascular surgical interventions on the venous system in the lower extremity compared with compression alone.**

Results: **We included 11 studies (seven RCTs and four observational studies) with moderate to increased risk of bias. The meta-analysis of all studies demonstrated increased healing rate (pooled risk ratio [RR], 1.06; 95% confidence interval [CI], 1.00-1.13; I^2 = 10%) and lower risk of recurrence (RR, 0.54; 95% CI, 0.34-0.85; I^2 = 27%) with open surgical procedures compared with compression. However, the meta-analysis of only RCTs showed no difference, possibly due to imprecision. The meta-analysis of three RCTs showed no difference in time to ulcer healing, −0.41 (95% CI, −0.89 to 0.07). Two studies of endovascular surgical procedures compared with compression showed no significant difference in ulcer healing (RR, 1.65; 95% CI, 0.43-6.32). One study of open surgical venous ligation and stripping compared with endovenous laser also showed no significant difference in ulcer recurrence (RR, 0.83; 95% CI, 0.21-3.27).**

Conclusions: **Open surgical interventions may improve lower extremity venous ulcer healing. The quality of this evidence is low because the analysis was dominated by the results of observational studies. The current evidence does not definitively support the superiority of endovascular surgical interventions compared with compression alone. (J Vasc Surg 2014;60:60S-70S.)**

Venous leg ulceration affects 500,000 to 2 million people annually in the United States, and the estimated prevalence in individuals aged >65 years is 1.7%.[1] The care of venous ulcer disease requires significant resources and cost.[2,3] Venous ulcer treatment has two objectives: to heal the ulcer and avoid ulcer recurrence.[4] The standard first-line clinical treatment is compression and debridement; when first-line treatment fails, multiple second-line treatments can be considered, but no widely accepted second-line treatment standard exists.

A common second-line treatment option is surgical treatment of the venous system. The variety of surgical treatment methods range from more invasive open surgical procedures, such as venous ligation and stripping, valvuloplasty, valve transplant/transposition, to less invasive open surgical procedures, such as subfascial endoscopic perforator surgery, and to less invasive endovenous surgical procedures, such as radiofrequency ablation, endovenous laser, sclerotherapy.

The specific type of surgical procedure offered varies depending on where the venous reflux exists (superficial reflux, perforator reflux, deep venous reflux, or any combination of these). Unfortunately, the evidence available to date does not clearly define which, if any, surgical treatment is more effective in improving ulcer healing and decreasing ulcer recurrence compared with compression alone. In this systematic review, we will summarize the evidence regarding the efficacy of surgical interventions compared with conservative management alone (compression) on ulcer healing and recurrence in patients with lower extremity ulceration due to venous disease.

METHODS

Search strategy. With the assistance of an expert librarian (L.P.), we designed and conducted an electronic search strategy, the details of which are available in the Appendix (online only). To identify potentially eligible studies, a comprehensive search of several databases from 1990 to December 2013 in any language was conducted. The databases included in the search were Ovid Medline In-Process & Other Non-Indexed Citations, Ovid

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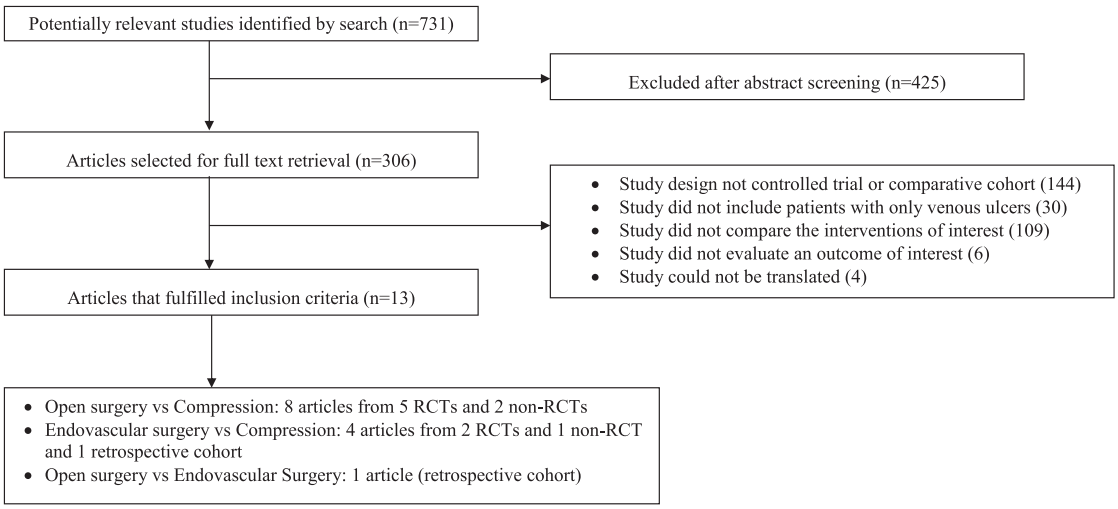

Fig 1. Study selection process. *RCT,* Randomized controlled trial.

MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. A controlled vocabulary supplemented with keywords was used to search for comparative studies of conservative therapy, surgery, and endovascular therapy for venous leg ulcers. We also performed a secondary hand search of the reference lists of all included studies as well as from previously published systematic reviews on this topic.

Study selection. References from the search were uploaded to Distiller SR (Evidence Partners Inc, Ottawa, Ontario, Canada), an online application designed specifically for the screening and data extraction phases of a systematic review. Two reviewers, working independently, screened all titles and abstracts for eligibility. References that were considered potentially relevant were retrieved in full text and again screened by two independent reviewers against the eligibility criteria. Disagreements were resolved by a third reviewer.

Two reviewers working independently used a standardized form to extract data from all eligible studies. Collected data included study description, methodologic quality assessment, and outcome data. These data were collated and any discrepancies were clarified by a third reviewer. We considered studies that included adults in any care setting who were described as having lower extremity ulcerations diagnosed as being due to venous disease, regardless of which method of diagnosis was used.

Excluded were studies that included individuals with lower extremity ulcerations due to other etiologies (eg, arterial, neuropathic, or vasculitis) and those that reported ulcers due to mixed etiologies and did not report outcome data separately for venous ulcers. We included any study that compared surgical intervention on the venous system in the lower extremity (open or endovascular) vs another surgical intervention or with compression alone. Compression treatment was defined as any method of compression. Surgical interventions at the site of the ulceration that did not involve the venous system were excluded.

For this review, we considered only those studies that compared one intervention with another in the form of randomized controlled trials (RCTs) or comparative cohort studies. We included any study (meeting abstract or published manuscript) from 1990 to November 2013 that reported the outcomes of interest in our defined study population. Studies were included regardless of sample size, surgical technique, duration of follow-up, or language of publication.

To be considered for inclusion, a study had to report at least one of the following outcomes: (1) ulcer healing (number of ulcers healed or number of limbs with ulcers healed), (2) time to ulcer healing, or (3) ulcer recurrence. We did not include studies that only reported changes in ulcer area or size because these outcomes are not as robust and patient-important as complete outcome healing.[5]

Validity assessment. Validity and methodological quality was assessed using the Cochrane risk of bias tool[6] to determine the following for RCTs:

- How the randomization sequence was generated, concealed, and whether the randomization successfully ensured no important differences between groups at baseline;
- How blinding was achieved and which individuals were blinded;
- How follow-up was assessed and reported; and
- How the analysis was reported.

We used the Newcastle-Ottawa Scale[7] to determine the following for cohort studies:

- Selection of study cohorts (how representative these cohorts were of patients of interest, whether adequate

Table I. Baseline characteristics of included studies

Name, study design, and follow-up period	*No. of patients (or limbs), age, sex, and ethnicity*	*Location/setting*	*Inclusion and exclusion criteria*	*Ulcer characteristics*	*Interventions (No. of patients, unless specified)*
Open or endovascular surgery vs compression					
Alden,[20] 2013 Cohort 12 months	86 patients: 95 ulcers 95 limbs Mean age: 69 years 53% male Ethnicity: NR	Hospital-based multidisciplinary wound clinic in the United States	Patients with chronic venous ulcer based on clinical criteria of ulcer location, stasis change and edema along with ultrasound evidence of venous insufficiency	Size: >2 cm Recurrence: Mixture of first time and recurrent ulcers. Venous system studied: Superficial and deep venous system and perforators. Amount of deep venous reflux: Superficial, deep and perforator reflux. Superficial reflux only, 17; perforator reflux only, 21; deep reflux only, 2; superficial and perforator, 44; superficial and deep, 3; superficial, deep and perforator, 8	Surgery (48 ulcers): Patients treated with compression and minimally invasive interventions, such as thermal ablation of superficial axial reflux and UGFS of incompetent perforating veins and varicosities, stab phlebectomies, or SFJ ligation under local anesthesia Compression (47 ulcers): Compression with multilayer semirigid dressings with 2- and 4-layer bandage systems, Unna boots, short stretch bandages, compression hosiery
Barwell,[18] 2000 Nonrandomized trial 36 months	236 limbs Median age: 73 years Gender: NR Ethnicity: NR	Community-based ulcer clinics in the United Kingdom	Inclusion: Patients with chronic leg ulceration (active ulcer) or an ulcer that has healed in the previous 6 months, ABPI >0.85, superficial venous reflux Exclusion: Patients with ABPI <0.85 and patients with deep or mixed venous reflux	Venous system studied: Superficial venous systems and perforators. Amount of deep venous reflux: None	Surgery (131 limbs): Patients who elected to have superficial venous surgery on long and/or SSV systems and/or both. Surgery was followed by compression stockings after ulcer healing. Compression (105 limbs): Patients who elected not to have surgery were given compression with 4-layer bandage
Barwell,[12] 2004 (ESCHAR) RCT 24 months Gohel,[11] 2007 (ESCHAR) RCT 48 months	500 patients Median age: 73 years 42% males	Nurse-led leg ulcer clinics in 3 vascular centers in the United Kingdom	Inclusion: Patients with open or recently healed (within the preceding 6 months), ulceration for >4 weeks between the knee and malleoli, ABPI >0.85, and superficial venous reflux alone or mixed superficial and deep venous reflux on duplex imaging Exclusion: Complete color duplex imaging was not practical, deep veins were occluded, unable to give informed consent, unfit for surgery even under local anesthetic, compression treatment was not practical, or the ulcer was of malignant cause	Size: Combination of >2 cm and <2 cm. Recurrence: Mixture of first time and recurrent ulcers. Venous system studied: Superficial and deep venous systems. Isolated superficial reflux, 300; superficial reflux with segmental deep reflux. 126); superficial with total deep reflux, 74	Surgery, 242: Open surgery (ligation of the GSV and/or SSV and stripping) + multilayered compression. Compression, 258: Open ulceration: Multilayered compression Healed ulcers: Class 2 elastic stocking
Guest,[10] 2003 RCT 6 months	76 patients/206 limbs Mean age: 69 years 49% Males	Outpatient leg ulcer clinic in the United Kingdom	Inclusion: Patients with leg ulceration with clinical evidence of venous disease, an ABPI of >0.8 and the absence of other etiological risk factors for ulceration Exclusion: Patients considered unfit for surgery; ulcers due to nonvenous etiology (arterial ulcers with ABPI <0.8, diabetes, seropositive arthritis, vasculitic ulcers, etc)	Size: Combination of >2 cm and <2 cm. Recurrence: Mixture of first time and recurrent ulcers. Location: 'Mixed medial and lateral. Venous system studied: Superficial incompetence, 12; superficial and deep incompetence, 12; superficial and perforator incompetence, 33; superficial, perforator and deep incompetence,19	Surgery, 37 limbs: Long saphenous ligation with stripping or sequential avulsion. Additional SSV ligation and perforator ligation or SEPS as indicated + 4-layer compression bandage Compression, 39 limbs: Four-layer compression bandage for 26 weeks, if no healing, then crossover to surgery allowed

Table I. Continued.

Name, study design, and follow-up period	*No. of patients (or limbs), age, sex, and ethnicity*	*Location/setting*	*Inclusion and exclusion criteria*	*Ulcer characteristics*	*Interventions (No. of patients, unless specified)*
O'Hare,[15] 2010 RCT 6 months	40 patients Median age: 69 years	Nurse-led leg ulcer clinic in United Kingdom	Inclusion: Patients with active venous ulcer, >1-sec retrograde flow on duplex in the GSV, SSV, anterior accessory saphenous vein, or other large superficial vein with significant proximal deep venous connection, without total deep venous incompetence Exclusion: ABPI <0.8, previous deep vein thrombosis or pulmonary embolism, poorly controlled diabetes, rheumatoid arthritis, malignancy, immobility, currently taking warfarin, and those unable to give informed consent.	Size: Combination of >2 cm and <2 cm. Recurrence: Mixture of first-time and recurrent ulcers. Venous system studied: Superficial venous system with or without significant proximal deep venous connection; without total deep venous incompetence	Surgery, 18: Foam sclerotherapy + compression with 4-layer bandage Compression, 22: Compression with 4-layer bandage
Queral,[16] 1990 Nonrandomized trial 1.5 months	25 patients Age: 32-68 years	University vascular surgical private outpatient vascular clinic, Maryland, US	Inclusion: Patients with active perimalleolar venous stasis ulceration diagnosed by physical examination. Presence of large venous channels immediately adjacent to the ulcer bed on portable Doppler supplemented digital examination. Exclusion: Deep venous thrombosis	Size: NR	Surgery, 12: Sotradecol sclerotherapy of adjacent veins + Unna compression boots. Compression, 13: Unna compression boots
Van Gent,[9] 2006 RCT 36 months (mean 27.5 months)	170 patients/200 limbs Mean age: 66 years 62% Males	12 centers in The Netherlands	Inclusion: Patients with open venous leg ulcers, unilateral or bilateral Exclusion: Patients with ABPI <0.8, total or partial occlusion of the deep venous system, former subfascial ligation of perforating veins, severe neurologic or muscular pathology, and immobility	Size: Combination of >2 cm and <2 cm. Location: Mixed medial and lateral. Recurrence: Mixture of first time and recurrent ulcers. Venous system studied: Superficial and deep venous system. Amount of deep venous reflux: Deep axial and segmental reflux were both considered deep reflux (54%)	Surgery (97 limbs): SEPS and concomitant superficial venous incompetence was also treated when indicated. Compression post-op with dual-layer short-stretch bandage. After ulcer healing, elastic stockings used. Compression, 103 limbs: Ambulatory compression therapy with dual-layer short-stretch bandage; elastic stockings used after ulcer healing
Viarengo,[14] 2007 RCT 12 months	52 patients Mean age: 59 years 25% Males	Vascular surgery outpatient facility at the Clinics Hospital of the Universidade Estadual de Campinas, Brazil	Inclusion: Consecutive patients with primary varicose veins in the lower limbs with active ulceration Exclusion: Patients with previous saphenectomy, acute deep venous thrombosis or superficial thrombophlebitis, occlusion of the femoral or iliac vein presenting with post-thrombotic syndrome, coagulation disorders, peripheral arterial disease, or degenerative systemic diseases, pregnant women, or unable to ambulate	Venous system studied: Superficial venous system and perforators Amount of deep venous reflux: NR	Surgery, 27: Endovenous laser therapy of the GSV, SSV, or both + elastic support. Compression, 25: Clinical treatment consisted of (1) dressing at home followed by elastic support or (2) Unna boot (according to medical recommendation)

(*Continued on next page*)

Table I. Continued.

Name, study design, and follow-up period	*No. of patients (or limbs), age, sex, and ethnicity*	*Location/setting*	*Inclusion and exclusion criteria*	*Ulcer characteristics*	*Interventions (No. of patients, unless specified)*
Vranic,[17] 2010 Nonrandomized trial 12 months	52 patients Mean age: 51 years 27% Males	Clinic of Orthopedics and Traumatology, Clinical Centre of Sarajevo University, Bosnia	Inclusion: Patients had stage III venous ulcers on the shin and preserved arterial circulation. Exclusion: Insufficient arterial circulation, diabetic, not cardiopulmonary and laboratory compensated.	Size: Combination of >2 cm and <2 cm. Venous system studied: Perforators. Amount of deep venous reflux: NR	Surgery, 26: Subfascial Cockett's ligation of perforating veins and post-op compressive elastic stocking. Compression, 26: Compressive elastic stocking, wound care, and antibiotics as indicated
Warburg,[8] 1994 RCT 12 months	32 patients Median age: 63 years 41% Males	Dermato-venerological department in a hospital in Denmark	Inclusion: Patients with lipodermatosclerosis, leg ulcers and adjacent incompetent perforating veins Exclusion: Significant arterial insufficiency of the leg, diabetes, rheumatoid arthritis, incompensated heart disease, walking impairment	Size: Combination of >2 cm and <2 cm. Venous system studied: Superficial venous system and perforators. Amount of deep venous reflux: NR	Surgery, 16: Surgery for incompetent perforators (or incompetent superficial vein) + hydrocolloid wound dressing and compression bandage. Compression, 16: Hydrocolloid wound dressing and compression bandage
Zamboni,[13] 2003 RCT 36 months	45 patients/47 limbs Mean age: 63 years 40% males	Day-Surgery Unit, University of Ferrara, Italy	Inclusion: Patients with primary SFJ and/or popliteal junction and GSV and/or SSV disease with unilateral or bilateral venous leg ulcers Exclusion: Patients aged >80 years, unable to walk, ulceration <2 cm^2 or >12 cm^2, diabetes, peripheral arterial disease and/or an ABPI <0.9, secondary or congenital venous disease	Size: >2 cm. Venous system studied: Superficial venous system. Amount of deep venous reflux: None	Surgery (21 patients/23 limbs): CHIVA 1: Classic high ligation of the SFJ and/or SPJ completed by flush ligation and division from the saphenous trunk and insufficient tributaries (for type 1 shunt) or CHIVA 2: Flush ligation and disconnection from the saphenous trunk of the insufficient tributaries with additional high ligation if needed (for type 3 shunt). Postoperative elastic stocking. Compression, 24 patients/24 limbs: Foam dressing, zinc oxide and inelastic bandage until healing, antibiotics as needed; elastic stockings after healing
Open surgery vs endovascular surgery					
Lakhwani,[19] 2009 Historical cohort 12 months	96 limbs with ulcers (350 limbs total in study) Mean age: 53 years 36% Males 93% Asians	Outpatient clinic of surgical department in Malaysia	Patients presenting to the outpatient clinic of the surgical department with SFJ and/or SPJ incompetence associated with reflux of the GSV or the SSV, respectively, who underwent varicose vein surgery or EVLT. For this review, we only included the 96 limbs that had active ulceration at the time of intervention. Exclusion: Nonpalpable pedal pulses or peripheral arterial disease, inability to ambulate, deep venous thrombosis, general poor health, pregnancy, nursing, or plans to become pregnant during the course of investigation. Extremely tortuous GSV in the EVLT group	Venous system studied: Superficial venous system. Amount of deep venous reflux: None	Open surgery, 64 limbs: Varicose vein surgery (ligation, stripping and avulsion) Endovascular surgery, 32 limbs: EVLT

ABPI, Ankle-brachial pressure index; *CHIVA,* Conservative Hemodynamic treatment of Insufficiency of the venous system in an Ambulatory setting; *EVLT,* endovenous laser therapy; *ESCHAR,* Effect of Surgery and Compression on Healing and Recurrence; *GSV,* great saphenous vein; *NR,* not reported; *RCT,* randomized controlled trial; *SEPS,* subfascial endoscopic perforating vein surgery; *SFJ,* saphenofemoral junction; *SPJ,* saphenopopliteal junction; *SSV,* small saphenous vein; *UGFS,* ultrasound-guided foam sclerotherapy.

ascertainment of the exposures and outcomes at baseline was conducted);
- Comparability of study cohorts by means of matching or statistical adjustment by key predictors of outcome; and
- Ascertainment of outcome (planning long enough follow-up to allow time for critical outcomes to develop, blinding the assessment of outcomes in both groups, etc.).

Statistical analysis. Results were grouped according to the types of interventions compared. Statistical pooling of outcome data was performed using Comprehensive Meta-Analysis 2 software (Biostat, Englewood, NJ). Because we anticipated significant heterogeneity between the studies given variable types of surgical interventions and variable types of compression, we presented all data using a random effects model. Sensitivity analyses were performed with poorly designed studies (with a high risk of biased results as determined by our validity assessment described above) removed. Subgroup analyses on outcomes in the following subgroups were also planned: ulcer size (<2 cm vs ≥2 cm), medial vs lateral ulcers, first-time ulcers vs recurrent ulcers, specific type of surgical intervention, and presence of deep venous system involvement vs superficial venous involvement alone. Unfortunately, too few studies reported separate outcomes for these variables, so many of these subgroup analyses were not performed.

RESULTS

Study selection, characteristics, and methodologic quality

The initial search revealed 731 citations, from which 306 were selected for full text retrieval and review. Of those articles excluded after full text screening, 144 studies were excluded because the study design was not a controlled trial or comparative cohort, 30 did not include patients with only venous ulcers, 109 did not compare the interventions of interest, 6 did not evaluate an outcome of interest, and 4 could not be translated. We identified 13 eligible articles that represented 12 unique studies (Fig 1). Eight articles reported results from seven RCTs,[8-15] three reported results from nonrandomized trials,[16-18] and two reported results from historical comparative cohorts.[19,20] Results were reported on 1451 ulcerated limbs (the number of patients were not available from all studies because some studies only reported the number of limbs). Table I summarizes the characteristics of the included studies. The risk of bias was moderate to high across the studies. A quality assessment of the included studies is summarized in Table II.

Open surgical procedures vs compression

Ulcer healing outcomes. Seven studies (eight articles) compared open surgical procedures on the venous system (with or without compression) with compression alone on ulcer healing outcomes, representing 572 limbs in the surgical group and 571 limbs in the compression group.[8-13,17,18] Barwell et al[12] and Gohel et al[11] reported 12-month and 48-month outcomes, respectively, from the same study. For the analysis, we included only the 48-month outcomes from Gohel et al.[11] The pooled risk ratio (RR) was 1.06 (95% confidence interval [CI], 1.00%-1.13%; $I^2 = 9.9$), demonstrating that ulcer healing outcomes are only slightly better in the surgery group (Fig 2). There was no difference in ulcer healing outcomes when only RCTs were included[8-11,13] (pooled RR, 1.04; 95% CI, 0.98-1.09; $I^2 = 0.0$; Fig 3). Similarly, excluding the study by Barwell et al[12] without compression provided to the control group did not change our conclusions.[18]

Ulcer recurrence outcomes. Three studies compared ulcer recurrence outcomes, representing 507 limbs in the surgical group and 380 limbs in the compression group.[9,11,18] The pooled RR was 0.54 (95% CI, 0.34-0.85; $I^2 = 26.6$), indicating that surgical intervention resulted in less ulcer recurrence (Fig 4). When only RCTs were included, there was a trend toward surgical intervention resulting in less ulcer recurrence, but this was no longer statistically significant (RR, 0.67; 95% CI, 0.41-1.10; $I^2 = 0.0$; Fig 5).[9,11]

Time to ulcer healing. Three articles reported time to ulcer healing outcomes, representing 150 limbs in the surgical group and 158 limbs in the compression group.[8-10] All were RCTs. The pooled difference in means was −0.41 months (95% CI, −0.89 to 0.07; $P = .10$), indicating no significant difference (Fig 6).

Endovascular surgical procedures vs compression

Ulcer healing outcomes. Two RCTs and an historical cohort study compared endovascular surgical procedures (with or without compression) vs compression alone on ulcer healing outcomes, representing 93 patients in the endovascular surgical group and 94 in the compression group.[14,15,20] The pooled RR was 1.29 (95% CI, 0.76-2.19; $I^2 = 51.7$), indicating no difference in ulcer healing outcomes between the two groups (Fig 7).

Ulcer recurrence. Outcomes on ulcer recurrence were also reported in the study by Alden et al.[20] Ulcer recurrence ≤1 year of healing occurred in 11 of 42 patients in the endovascular surgery group vs 23 of 40 in the compression group, suggesting a benefit of endovascular surgical intervention in reducing venous ulcer recurrence.

Time to ulcer healing. One study compared a variety of endovascular surgical procedures vs compression and reported the median time to ulcer healing was 7.9 weeks (interquartile range, 8.1 weeks) in the surgery group vs 22.0 weeks (interquartile range, 44.7 weeks), indicating that endovascular surgery was superior to compression alone.[20]

Open surgical procedures vs endovascular surgical procedures

Ulcer recurrence outcomes. Only one study compared open surgical venous ligation and stripping with endovenous laser, representing 64 limbs in the open surgery group and 32 limbs in the endovascular group.[19] The RR was 0.83 (95% CI, 0.21-3.27), indicating no difference

Table II. Quality of included studies

Controlled trials

Study	*Randomization, method*	*Allocation, concealment method*	*Blinding*	*Baseline imbalance*	*Lost to follow-up, %*	*Funding source*
Barwell,[18] 2000	No, patient self-selected intervention	No	No	Yes, patients in the surgery group were slightly younger and more mobile	NR	NR
Barwell,[12] 2004 (ESCHAR 12 months) Gohel,[11] 2007 (ESCHAR 48 months)	Yes, computer generated, stratified by superficial or mixed venous reflux	Yes, sequentially numbered, sealed envelopes	No	Yes, patients with diabetes in 10% of the compression group vs 5% in the surgery group	10% at 12 months; 11% at 48 months	Nonprofit
Guest,[10] 2003	Yes, sealed envelopes	Yes, sealed envelopes	No	No imbalance	4%	NR
O'Hare,[15] 2010	Yes, computer generated	Yes, sealed envelopes	NR	NR	18%	Nonprofit
Queral,[16] 1990	No, patients were alternately assigned	NR	NR	NR	NR	NR
Van Gent,[9] 2006	Yes, computer randomization center, stratified by first-time ulcer or recurrent, presence or absence of deep venous incompetence and center	Yes, method not specified	NR	No imbalance	2.3%	Nonprofit
Viarengo,[14] 2007	Yes, method not specified	NR	NR	No imbalance	NR	NR
Vranic,[17] 2010	No, patients were divided into 2 groups	NR	NR	No imbalance	NR	NR
Warburg,[8] 1994	Yes, method not specified	NR	NR	No imbalance	16%	NR
Zamboni,[13] 2003	Yes, computer randomization in blocks of 4	NR	NR	NR	0%	NR

Cohort studies

Study	*Representativeness of exposed cohort*	*Selection of the nonexposed cohort*	*Ascertainment of exposure*	*Outcome of interest was not present at start of study*	*Comparability of cohorts*	*Assessment of outcomes*	*Adequacy of follow-up*
Alden,[20] 2013	Patients were those who presented to the outpatient ulcer clinic for treatment	Drawn from the same group as the exposed cohort	Exposure was determined by the type of treatment for venous ulceration the patient received	No healed ulcers were present at the start of the study	No significant differences in the two cohorts	Ulcers healed, time to ulcer healing, recurrence of ulcers	Adequate, all patient records were reviewed at 1 year
Lakhwani,[19] 2009	Unclear; this was a convenience sample of patients who presented to clinic for treatment	Drawn from the same group as the exposed cohort	Exposure was determined by the type of surgical intervention offered	Yes, for a subset of the patients (this study included patients with and without ulcers; we considered only those patients with active ulcers at the time of presentation)	More venous ulcers in the open surgery group (32%) vs the endovenous laser group (21%)	Recurrent ulceration reported, but not clearly defined	Adequate, all patient records were reviewed at 1 year after procedure

NR, Not reported.

in ulcer recurrence outcomes between the two groups. This study was a retrospective cohort study, and no outcomes for ulcer healing or time to ulcer healing were reported.

Assessment of bias

Publication bias could not be reliably assessed due to the small number of included studies.

DISCUSSION

In this review, we systematically identified and summarized the evidence regarding the efficacy of surgical interventions (open surgery or endovascular surgery or procedure) compared with conservative management (compression) on ulcer healing and recurrence in patients with lower extremity ulceration due to venous disease. We also summarized the evidence of open surgical procedures compared with endovascular surgical procedures on similar outcomes. Only 12 unique studies met our eligibility criteria. Meta-analysis did not demonstrate a statistically significant effect to favor open or endovascular interventions over compression for ulcer healing, recurrence, or time to heal.

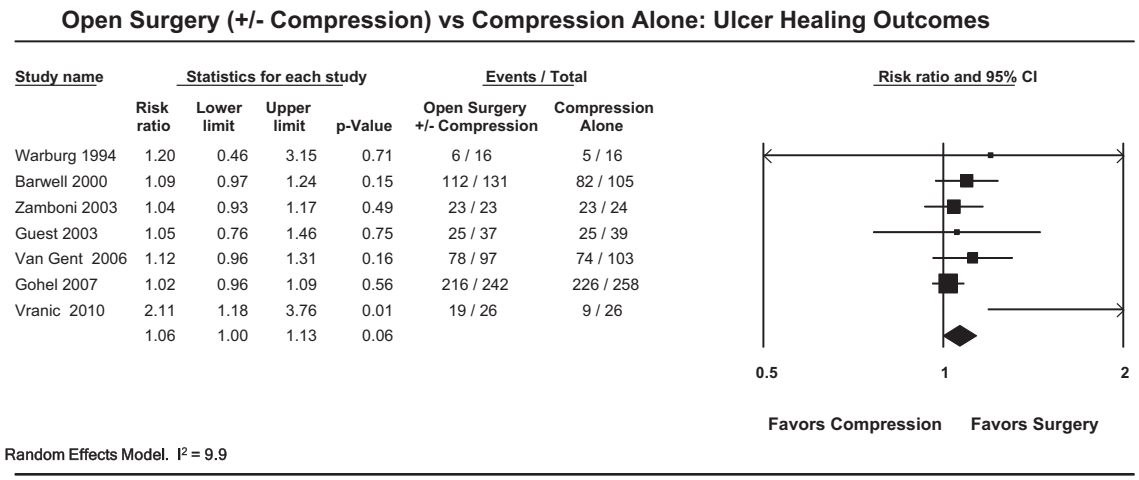

Fig 2. Forest plot shows results of meta-analysis of open surgical procedures, with or without compression, compared with compression alone on ulcer healing outcomes, with all studies included. The *solid squares* denote the relative risk, the *horizontal lines* represent the 95% confidence intervals (*CIs*), and the *diamond* denotes the pooled relative risk.

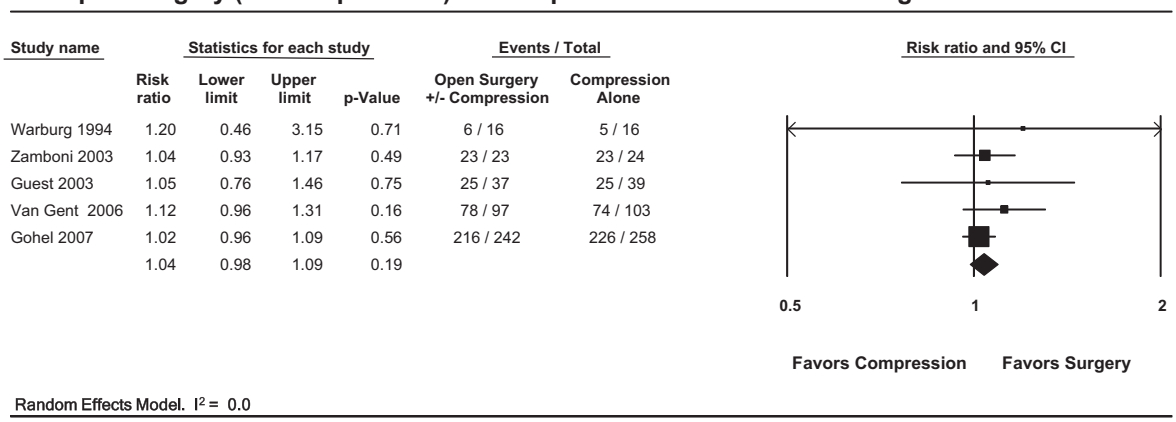

Fig 3. Forest plot shows results of meta-analysis of open surgical procedures, with or without compression, compared with compression alone on ulcer healing outcomes, with nonrandomized studies excluded. The *solid squares* denote the relative risk, the *horizontal lines* represent the 95% confidence intervals (*CIs*), and the *diamond* denotes the pooled relative risk.

The quality of evidence available for this review was quite low. Although much of the evidence was derived from trials, the quality of these studies was limited by lack of randomization[16-18] or the unclear description of randomization methods,[8,14] by lack of allocation concealment,[9,18] and by the lack of blinding in all studies. The types of interventions (surgical as well as compression) varied significantly across studies, and the number of patients in each study was small, which contributed to significant heterogeneity and imprecision, respectively.

The strengths of this review are the comprehensive literature search strategy and the inclusion of randomized trials, nonrandomized trials, and observational comparative cohort studies in an attempt to collect all available evidence. The outcomes chosen were those that were clinically important and clearly defined. Rigorous methodology was used in all steps of the data review and extraction process, which was conducted in duplicate by two independent reviewers with good interobserver agreement.

There was significant variation in the type of "open surgical procedures" included in this review. Although some surgical procedures included only ligation and stripping of the great saphenous vein (GSV) or small saphenous vein (SSV), or both, other studies included treatment of incompetent perforating veins (ICPVs), and some included surgical procedures that included a combination of both.

O'Donnell[21] has suggested that there is indirect evidence to suggest that ICPV ablation adds little additional benefit to the treatment of the GSV alone. The largest RCT, Effect of Surgery and Compression on Healing and Recurrence (ESCHAR), compared ligation and stripping of the GSV with or without SSV (without any ICPV ablation) with compression alone. Although initial ulcer

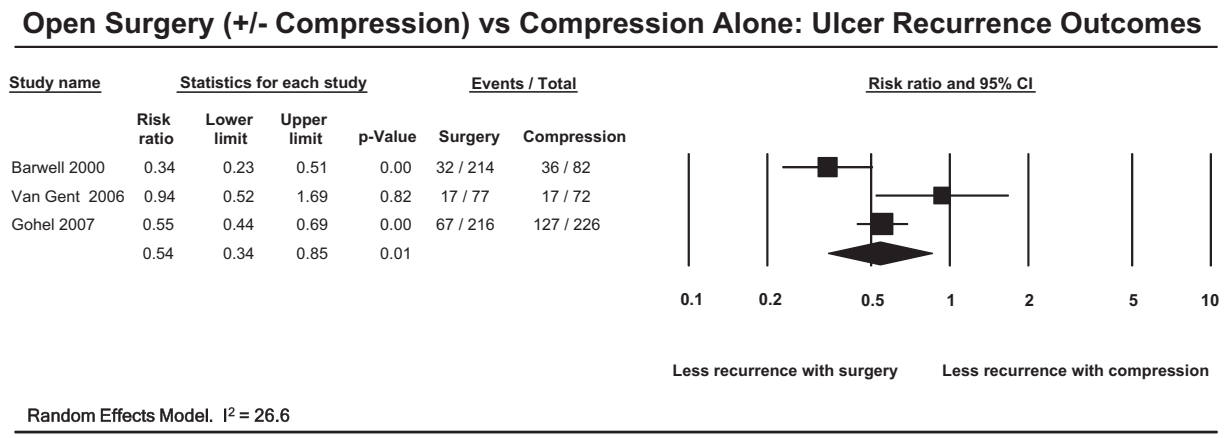

Fig 4. Forest plot shows meta-analysis of open surgical procedures, with or without compression, compared with compression alone on ulcer recurrence outcomes, with all studies included. The *solid squares* denote the relative risk, the *horizontal lines* represent the 95% confidence intervals (*CIs*), and the *diamond* denotes the pooled relative risk.

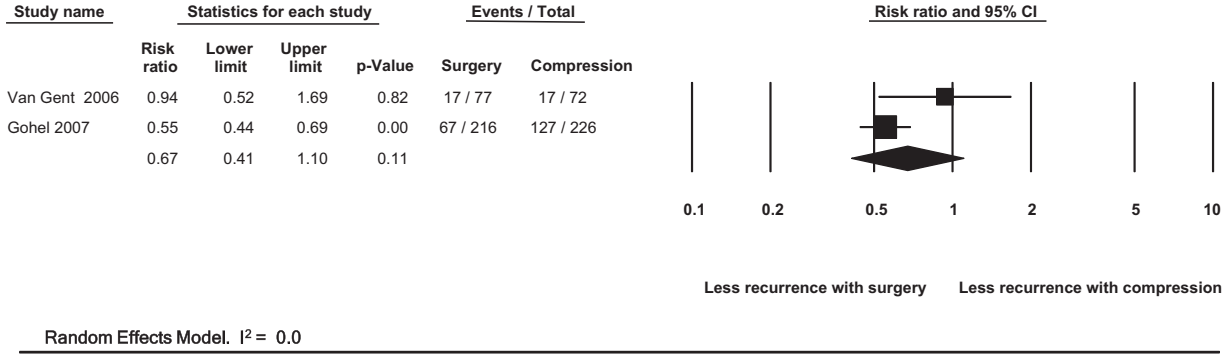

Fig 5. Forest plot shows results of meta-analysis of open surgical procedures, with or without compression, compared with compression alone on ulcer recurrence outcomes, with nonrandomized studies excluded. The *solid squares* denote the relative risk, the *horizontal lines* represent the 95% confidence intervals (*CIs*), and the *diamond* denotes the pooled relative risk.

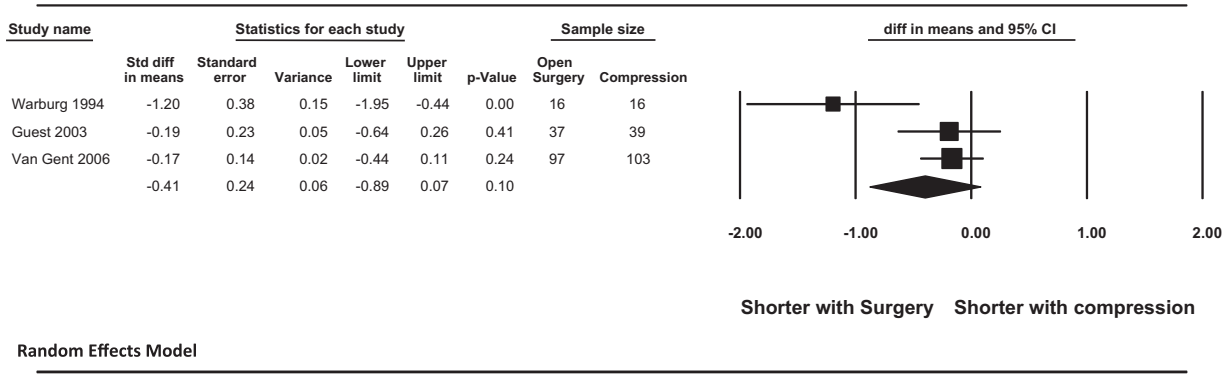

Fig 6. Forest plot shows results of meta-analysis of open surgical procedures, with or without compression, compared with compression alone on time in months to ulcer healing outcomes. The *solid squares* denote the mean difference, the *horizontal lines* represent the 95% confidence intervals (*CIs*), and the *diamond* denotes the weighted mean differences.

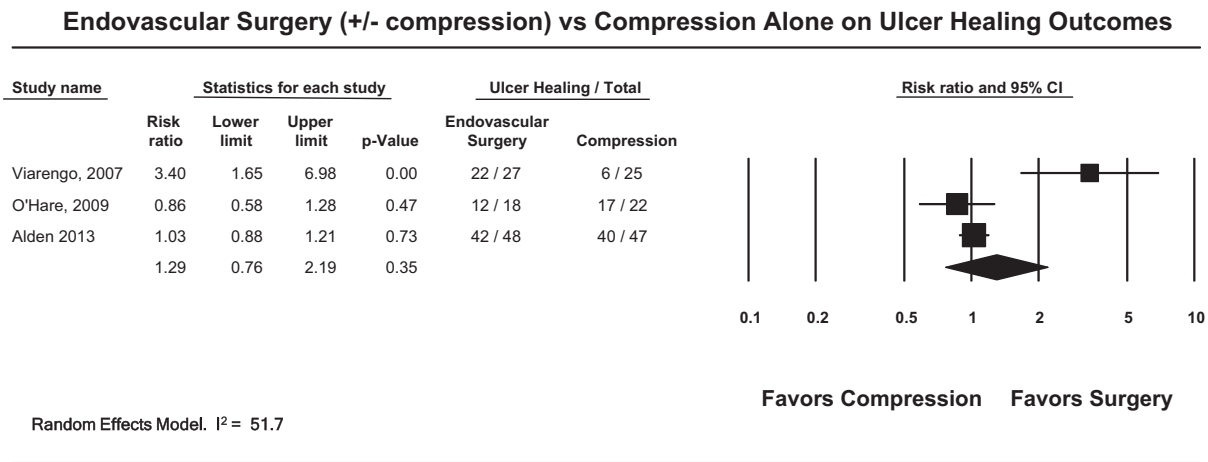

Fig 7. Forest plot shows results of meta-analysis of endovascular surgery compared with compression alone on ulcer healing outcomes, with all studies included. The *solid squares* denote the relative risk, the *horizontal lines* represent the 95% confidence intervals (*CIs*), and the *diamond* denotes the pooled relative risk.

healing did not differ significantly in the two arms, ulcer recurrence was significantly reduced in the surgical arm, and this benefit persisted after long-term follow-up.

Van Gent et al[9] also conducted a RCT in which surgical treatment was compared with compression alone. In their trial, however, the surgical treatment was subfascial endoscopic perforating vein surgery alone or combined with ligation and stripping of the GSV, when indicated. Their study found no difference in ulcer healing and no difference in ulcer recurrence. If the surgical treatment of perforating veins truly adds no benefit with respect to ulcer recurrence, then the results of this study would dilute the potential real benefit of ligation and stripping of the GSV on ulcer recurrence outcomes in our pooled analysis of the data.

CONCLUSIONS

The current evidence does not definitively support the superiority of open or endovascular surgical interventions compared with compression alone with respect to ulcer healing and ulcer recurrence outcomes in patients with lower extremity venous ulcers.

AUTHOR CONTRIBUTIONS

Conception and design: KM, NA, CU, TE, MN, OA, MS, LP, MM
Analysis and interpretation: KM, MM
Data collection: KM, NA, CU, TE, MN, OA, MS, LP
Writing the article: KM, NA, CU, TE, MN, OA, MS, LP, MM
Critical revision of the article: KM, NA, CU, TE, MN, OA, MS, LP, MM
Final approval of the article: KM, NA, CU, TE, MN, OA, MS, LP, MM
Statistical analysis: KM, MM
Obtained funding: MM
Overall responsibility: MM

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Additional material for this article may be found online at www.jvascsurg.org.

APPENDIX (online only). Search strategy

Ovid

Database(s): Embase 1988 to 2012 week 39; Ovid MEDLINE in-process and other NonIndexed Citations and Ovid MEDLINE 1946 to present; EBM Reviews—Cochrane Central Register of Controlled Trials, September 2012; EBM Reviews—Cochrane Database of Systematic Reviews, 2005 to September 2012 Search Strategy:

#	*Searches*	*Results*
1	exp Varicose Ulcer/dh, dt, pc, rt, rh, su, th [diet therapy, drug therapy, prevention & control, radiotherapy, rehabilitation, surgery, therapy]	2284
2	exp ulcer/dm, dt, pc, rt, rh, su, th [disease management, drug therapy, prevention, radiotherapy, rehabilitation, surgery, therapy]	46961
3	exp leg ulcer/	24470
4	(((venous or varicose or stasis) adj2 ulcer*) and (leg or legs)).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui, tx, ct]	6298
5	(1 or 2) and 3	6078
6	4 or 5	10012
7	exp varicose ulcer/su [Surgery]	8250
8	exp ulcer/su [Surgery]	13360
9	(surgery or surgical or flap or flaps or transplant* or debridement).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui, tx, ct]	3809796
10	or/7-9	3816572
11	exp ablation techniques/	89784
12	exp ablation therapy/	3693
13	exp radiofrequency ablation/	12280
14	exp laser surgery/	91361
15	exp catheter ablation/	38080
16	exp cyanoacrylate/	5237
17	exp sclerotherapy/	13045
18	(endovenous or endovascular or ablation or ablative or "radio frequency" or radiofrequency or laser* or steam or clarivein or Cyanoacrylate or glue or sclerotherap* or sclerosation or sclerozation or (sclerosing adj2 (therap* or care or treatment*))).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui, tx, ct]	635044
19	or/11-18	657430
20	exp stockings, compression/	2683
21	exp compression therapy/	5724
22	exp conservative treatment/	289945
23	("standard management" or "standard care" or "standard therap*" or "standard treatment*" or "conventional management" or "conventional care" or "conventional therap*" or "conventional treatment*" or "conservative management" or "conservative care" or "conservative therap*" or "conservative treatment*").mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui, tx, ct]	199171
24	(compression or bandage* or stocking* or dressing* or Unna or Unnas or "circ-aid" or circaid).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui, tx, ct]	224681
25	or/20-24	660352
26	6 and 10 and (19 or 25)	1620
27	6 and 19 and 25	378
28	26 or 27	1760
29	exp controlled study/	3943648
30	exp randomized controlled trial/	651961
31	((control$ or randomized) adj2 (study or studies or trial or trials)).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui, tx, ct]	5050079
32	meta analysis/	102969
33	meta-analys$.mp.	165476
34	exp "systematic review"/	53391
35	(systematic* adj review$).mp.	125284
36	exp cohort studies/	1441721
37	exp longitudinal study/	936912
38	exp retrospective study/	716957
39	exp prospective study/	596445
40	exp comparative study/	2334016
41	exp clinical trial/	1592689
42	((clinical or comparative or cohort or longitudinal or retrospective or prospective or concurrent) adj (study or studies or survey or surveys or analysis or analyses or trial or trials)).mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui, tx, ct]	6339437
43	or/29-42	9900498
44	28 and 43	850
45	from 28 keep 1044-1648	605
46	limit 45 to (clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or comparative study or controlled clinical trial or meta analysis or randomized controlled trial) [Limit not valid in Embase, CCTR, CDSR; records were retained]	150
47	44 or 46	850
48	limit 47 to (book or book series or editorial or erratum or letter or note or addresses or autobiography or bibliography or biography or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase, Ovid MEDLINE, Ovid MEDLINE In-Process, CCTR, CDSR; records were retained]	62
49	47 not 48	788
50	from 28 keep 1649-1760	112
51	49 or 50	849
52	limit 51 to year = "1990-Current"	819
53	remove duplicates from 52	616

Scopus

1	TITLE-ABS-KEY (((venous w/2 ulcer*) or (varicose w/2 ulcer*) or (stasis w/2 ulcer*)) and (leg or legs))
2	TITLE-ABS-KEY (surgery or surgical or flap or flaps or transplant* or debridement)
3	TITLE-ABS-KEY (endovenous or endovascular or ablation or ablative or "radio frequency" or radiofrequency or laser* or steam or clarivein or Cyanoacrylate or glue or sclerotherap* or sclerosation or sclerozation or (sclerosing w/2 therap*) or (sclerosing w/2 care) or (sclerosing w/2 treatment*))
4	TITLE-ABS-KEY ("standard management" or "standard care" or "standard therap*" or "standard treatment*" or "conventional management" or "conventional care" or "conventional therap*" or "conventional treatment*" or "conservative management" or "conservative care" or "conservative therap*" or "conservative treatment*" or compression or bandage* or stocking* or dressing* or Unna or Unnas or "circ-aid" or circaid)
5	1 and 2 and (3 or 4)
6	1 and 3 and 4
7	5 or 6
8	PUBYEAR >1989
9	7 and 8
10	TITLE-ABS-KEY((meta W/1 analys*) or (systematic* W/2 review*) or (control* W/2 stud*) or (control* W/2 trial*) or (randomized W/2 stud*) or (randomized W/2 trial*) or "comparative stud*" or "comparative survey*" or "comparative analys*" or "cohort stud*" or "cohort survey*" or "cohort analys*" or "longitudinal stud*" or "longitudinal survey*" or "longitudinal analys*" or "retrospective stud*" or "retrospective survey*" or "retrospective analys*" or "prospective stud*" or "prospective survey*" or "prospective analys*" or "concurrent stud*" or "concurrent survey*" or "concurrent analys*" or "clinical stud*" or "clinical trial*")
11	9 and 10
12	PMID(0*) or PMID(1*) or PMID(2*) or PMID(3*) or PMID(4*) or PMID(5*) or PMID(6*) or PMID(7*) or PMID(8*) or PMID(9*)
13	11 and not 12
14	DOCTYPE(le) or DOCTYPE(ed) or DOCTYPE(bk) or DOCTYPE(er) or DOCTYPE(no) or DOCTYPE(sh)
15	13 and not 14